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## (57) Abstract

Novel amide derivatives, processes for their preparation, pharmaceutical compositions containing them and their use as medicaments are disclosed.

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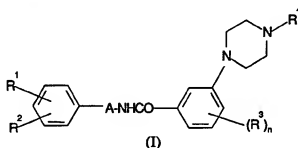
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Amide derivatives as 5HT<sub>1D</sub> receptor antagonists

The present invention relates to novel amide derivatives, processes for their preparation, and pharmaceutical compositions containing them.

- 5 EPA 0 533 266/7/8 disclose a series of benzanilide derivatives which are said to possess 5HT<sub>1D</sub> receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders.

- A structurally distinct class of compounds have now been discovered and have been found to exhibit 5HT<sub>1D</sub> antagonist activity. In a first aspect, the present invention  
10 therefore provides a compound of formula (I) or a salt thereof:



- 15 in which

R<sup>1</sup> is optionally substituted phenyl or an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur or R<sup>1</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>cycloalkyl, C<sub>1-6</sub>alkoxy, hydroxyC<sub>1-6</sub>alkyl, acyl, nitro, trifluoromethyl, cyano, SR<sup>5</sup>, SOR<sup>5</sup>, SO<sub>2</sub>R<sup>5</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, CO<sub>2</sub>R<sup>5</sup>, CONR<sup>5</sup>R<sup>6</sup>,  
20 CONR<sup>5</sup>(CH<sub>2</sub>)<sub>p</sub>CO<sub>2</sub>R<sup>6</sup>, NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>CO<sub>2</sub>R<sup>6</sup>, CR<sup>5</sup>=NOR<sup>6</sup>,

where R<sup>5</sup> and R<sup>6</sup> are independently hydrogen or C<sub>1-6</sub>alkyl and p is 1 to 3;

R<sup>2</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, hydroxyC<sub>1-6</sub>alkyl, acyl, nitro, trifluoromethyl, cyano, SR<sup>5</sup>, SOR<sup>5</sup>, SO<sub>2</sub>R<sup>5</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, CO<sub>2</sub>R<sup>5</sup>, CONR<sup>5</sup>R<sup>6</sup>,  
CONR<sup>5</sup>(CH<sub>2</sub>)<sub>p</sub>CO<sub>2</sub>R<sup>6</sup>, NR<sup>5</sup>R<sup>6</sup>, NR<sup>5</sup>CO<sub>2</sub>R<sup>6</sup>, CR<sup>5</sup>=NOR<sup>6</sup>,

- 25 where R<sup>5</sup>, R<sup>6</sup> and p are as defined for R<sup>1</sup>;

R<sup>3</sup> is hydrogen, halogen, hydroxy, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy;

R<sup>4</sup> is hydrogen or C<sub>1-6</sub>alkyl;

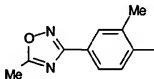
A is a bond or an acyclic hydrocarbon chain having 1 to 6 carbon atoms; and  
n is 1 or 2.

- 30 The group R<sup>1</sup> can be an aromatic or saturated heterocyclic ring. When R<sup>1</sup> is an aromatic heterocyclic ring, examples of such rings include thienyl, furyl, pyrrolyl, triazolyl, diazolyl, isothiazolyl, oxadiazolyl, isoxazolyl, thiadiazolyl, pyrimidyl and pyrazinyl. When R<sup>1</sup> is a saturated ring examples include piperidine, morpholine and

piperazine rings. The group  $R^1$  can be linked to the remainder of the molecule via a carbon atom or, when present, a nitrogen atom.

Preferably the group  $R^1$  is attached to the 4-position of the phenyl ring, that is to say, para to the amide group. Optional substituents for  $R^1$  heterocyclic rings include  
 5 halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, hydroxy, cyano, nitro, amino,  $CO_2R^5$  or  $CONR^5R^6$  where  $R^5$  and  $R^6$  are independently hydrogen or  $C_{1-6}$ alkyl.  $R^1$  phenyl groups can be mono or di-substituted. Optional substituents for  $R^1$  phenyl groups include halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, hydroxy, cyano, nitro, amino,  $CO_2R^5$  or  $CONR^5R^6$  where  $R^5$  and  $R^6$  are independently hydrogen or  $C_{1-6}$ alkyl as well as 5 to 7-membered heterocyclic  
 10 rings containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. These heterocyclic rings can themselves be substituted, for example by  $C_{1-6}$ alkyl.

Preferably  $R^1$  is halogen, cyclohexyl, optionally substituted pyridyl or optionally substituted phenyl. More preferably  $R^1$  is phenyl disubstituted by a  $C_{1-6}$ alkyl group and a 1,2,4-oxadiazol-3-yl group, in particular disubstituted by a methyl and a 5-methyl-1,2,4-oxadiazol-3-yl group. Most preferably  $R^1$  is a group of formula:



Suitably  $R^2$  is hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, hydroxy,  $C_{1-6}$ alkyl, acyl, nitro, trifluoromethyl, cyano,  $SR^5$ ,  $SOR^5$ ,  $SO_2R^5$ ,  $SO_2NR^5R^6$ ,  $CO_2R^5$ ,  $CONR^5R^6$ ,  $CONR^5(CH_2)_pCO_2R^6$ ,  $NR^5R^6$ ,  $NR^5CO_2R^6$ ,  $CR^5=NOR^6$  where  $R^5$  and  $R^6$  are independently hydrogen or  $C_{1-6}$ alkyl and  $p$  is 1 to 3. Preferably  $R^2$  is hydrogen or  $C_{1-6}$ alkyl, for example methyl.

Suitably  $R^3$  is hydrogen, halogen, hydroxy,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy. Preferably  
 25  $R^3$  is  $C_{1-6}$ alkoxy such as methoxy.

Preferably  $n$  is 1.

Suitably  $R^4$  is hydrogen or  $C_{1-6}$ alkyl. Preferably  $R^4$  is  $C_{1-6}$ alkyl such as methyl.

For the avoidance of doubt, the term 'chain of 1 to 6 carbon atoms' means carbon atoms extending in a branched or unbranched chain between the phenyl group and the  
 30 amide group. The hydrocarbon chain can be an alkylene chain, for example methylene or ethylene, or A can contain alkene or alkyne groups. For example, the group A can be methylene or ethylene. Preferably A is a bond.

$C_{1-6}$ alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Particularly preferred compounds include:

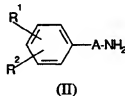
4-methoxy-3-(4-methyl-1-piperazinyl)-N-(4-bromo-3-methylphenyl)benzamide,  
 4-methoxy-3-(4-methyl-1-piperazinyl)-N-(4-bromophenyl)benzamide,  
 4-methoxy-3-(4-methyl-1-piperazinyl)-N-[3-methyl-4-(4-pyridyl)phenyl]benzamide,  
 4-methoxy-3-(4-methyl-1-piperazinyl)-N-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)  
 (1,1'-biphenyl)]benzamide, or  
 4-methoxy-3-(4-methyl-1-piperazinyl)-N-(4-cyclohexylphenyl)benzamide,  
 or pharmaceutically acceptable salts thereof.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

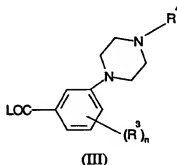
Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates. Tautomers of compounds of formula (I) and mixtures thereof also form part of the invention.

In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises.

(a) reaction of a compound of formula (II):

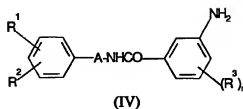


in which  $R^1$ ,  $R^2$  and A are as defined in formula (I), with a compound of formula (III):



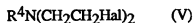
in which  $R^3$ ,  $R^4$  and n are as defined in formula (I) and L is a leaving group; or

(b) reaction of a compound of formula (IV):



5

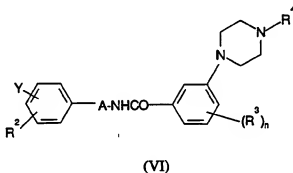
in which  $R^1$ ,  $R^2$ ,  $R^3$ , A and n are as defined in formula (I) with a compound of formula (V):



10

in which  $R^4$  is as defined in formula (I) and Hal is halogen, or

(c) reaction of a compound of formula (VI):



15

in which  $R^2$ ,  $R^3$ ,  $R^4$ , A and n are as defined in formula (I) and Y is halogen or a group -  
 20  $OSO_2CF_3$  with a compound of formula (VII):

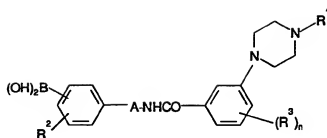


(VII)

25

in which  $R^1$  is as defined in formula (I), or

(d) reaction of a compound of formula (VIII):



(VIII)

- 5 in which  $R^2$ ,  $R^3$ ,  $R^4$ , A and n are as defined in formula (I) with a compound of formula (IX):

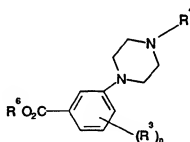


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(IX)

in which  $R^1$  is as defined in formula (I) and Y is as defined in formula (VI), or

- (e) reaction of a compound of formula (II) as defined above with a  
15 compound of formula (X):



(X)

20

in which  $R^3$ ,  $R^4$  and n are as defined in formula (I) and  $R^6$  is  $C_{1-4}$ alkyl in the presence of a trialkylaluminium reagent;  
and optionally after any of the above processes:

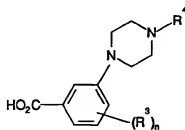
- 25
- converting a compound of formula (I) into another compound of formula (I)
  - forming a pharmaceutically acceptable salt.

Suitable activated carboxylic acid derivatives of formula (III) include acyl halides and acid anhydrides. Activated compounds of formula (III) can also be prepared by reaction of the corresponding carboxylic acid with a coupling reagent such as

carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazole. Preferably the group L is halo, particularly chloro.

A compound of formula (II) is typically reacted with a compound of formula (III) in an inert organic solvent such as DMF, THF or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

Compounds of formula (III) can be prepared from a compound of formula (XI):



(XI)

in which R<sup>3</sup>, R<sup>4</sup> and n are as defined in formula (I) using standard procedures. For example acid chlorides can be prepared by reaction with phosphorous pentachloride, oxalyl chloride or thionyl chloride. Acid anhydrides can be prepared by reaction with a suitable acid anhydride, for example trifluoroacetic anhydride.

Reaction of a compound of formula (IV) with a compound of formula (V) is suitably carried out in an alcohol or nitrile solvent with an optional base or, alternatively, in a non-polar solvent such as chlorobenzene in the absence of base. Suitably, the reactions are carried out at ambient or elevated temperature, preferably at the reflux temperature of the reaction mixture.

Reaction of compounds of formula (VI) and (VII) and reaction of compounds of formulae (VIII) and (IX) can be carried out in the presence of a transition metal catalyst such as Pd(PPh<sub>3</sub>)<sub>4</sub> in a solvent such as an ether in the presence of a base such as an alkali metal carbonate or bicarbonate, for example sodium carbonate or bicarbonate, at ambient or elevated temperature.

Compounds of formula (II) can be reacted with compounds of formula (X) in an organic solvent such as toluene in an inert atmosphere in the presence of a trialkylaluminium reagent, for example trimethylaluminium.

Intermediate compounds of formulae (II), (IV), (V), (VI), (VII), (VIII), (IX), (X) and (XI) are either commercially available or can be prepared using standard procedures. Certain intermediate compounds of formulae (II), (IV), (V), (VI), (VII), (VIII), (IX), (X) and (XI) are novel and form a further aspect of the invention.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures, for example when the



group R<sup>4</sup> is a hydrogen atom. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures.

- 5 Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

- Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, in the case wherein R<sup>4</sup> is hydrogen, it is possible to introduce a C<sub>1</sub>-alkyl group by conventional alkylation using 1 molar equivalent of a C<sub>1</sub>-alkyl halide and 1 molar equivalent of a suitable base in an inert solvent. Compounds of formula (I) in which R<sup>1</sup> or R<sup>2</sup> are acid groups can be esterified using normal procedures.

- 15 5HT<sub>1D</sub> Antagonists, and in particular the compounds of the present invention, are expected to be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal affective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; and disorders of eating behaviours, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

- 25 5HT<sub>1D</sub> Antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, in the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

- Therefore, the present invention, provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

- 30 The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

- In another aspect the invention provides the use of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of the aforementioned disorders.

- 35 In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such

treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be

accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

- 5       The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

- 10       The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

- 15       The following Examples illustrate the preparation of pharmacologically active compounds of the invention.

### Description 1

#### Methyl 4-methoxy-3-(4-methyl-1-piperazinyl)benzoate

Methyl 4-hydroxy-3-nitrobenzoate (5.00g, 0.025mol), was dissolved in acetone (100 ml),  
5 and treated with anhydrous potassium carbonate (6.91g, 0.050mol), followed by  
iodomethane (1.71 ml, 0.0275mol). The mixture was then heated to reflux with stirring.  
After 16h, more iodomethane (1.71 ml, 0.0275mol) was added and reflux was maintained  
for a further 3h. The reaction mixture was then filtered and the filtrate evaporated under  
10 reduced pressure to give an orange solid, which was dried *in vacuo*. The solid was then  
suspended in ethanol (200 ml), and was hydrogenated at atmospheric pressure in the  
presence of 5% Pd/C catalyst (0.5g). After 16h, the reaction mixture was filtered through  
kieselguhr and evaporated under reduced pressure to give a pale yellow oily solid, which  
was dried *in vacuo*. The oily solid was dissolved in chlorobenzene (50 ml), and  
15 methchloroethamine hydrochloride (14.44g, 0.075mol) was added. The reaction mixture was  
then heated to reflux under argon. After 30h, the reaction mixture was allowed to cool,  
and was left for a further 24h at room temperature before being evaporated under reduced  
pressure and partitioned between potassium carbonate solution and dichloromethane. The  
aqueous layer was then extracted with dichloromethane, and the combined organic layers  
20 were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to give a brown oily solid,  
which was dried *in vacuo*, and purified by silica gel chromatography (5% MeOH/ $\text{CH}_2\text{Cl}_2$ )  
to give the title compound (0.740g, 11%) as a brown oil.

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ),  $\delta$  7.75 (dd, 1H), 7.61 (s, 1H), 6.86 (d, 1 H), 3.93 (s, 3H),  
3.87 (s, 3H), 3.14 (br s, 4H), 2.65 (br s, 4H), 2.38 (s, 3H).  
25

### Example 1

#### 4-Methoxy-3-(4-methyl-1-piperazinyl)-N-(4-bromo-3-methylphenyl)benzamide

4-Bromo-3-methylaniline (0.2g, 1.08 mmol) was dissolved in dry toluene (10 ml) and  
treated with trimethylaluminium (2.0 M in toluene) (2.16ml, 4.32 mmol) with stirring  
under argon. After 0.25h, a solution of the product from description 1 (0.285g, 1.08mmol)  
in toluene (5 ml) was added. The mixture was then stirred at room temperature for 2h,  
before being heated to 80°C. After 2 h at 80°C, the reaction mixture was allowed to cool  
35 and was treated with dilute HCl, until no more effervescence took place. The reaction  
mixture was then partitioned between dichloromethane and water. The aqueous layer was  
then treated with aq. sodium bicarbonate until basic and then extracted with

dichloromethane (2X). The combined organic layers were then dried ( $\text{Na}_2\text{SO}_4$ ), and evaporated under reduced pressure to give a pale brown solid. The solid was the purified by silica-gel chromatography (6%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) as eluant, to give the title compound as a cream coloured foam (0.210g, 47%), which was converted to its oxalate salt.

5

m.pt 144-145°C

$^1\text{H}$  NMR (200MHz,  $\text{CDCl}_3$ )-free base- $\delta$  7.92 (s, 1H), 7.62 (d, 1H), 7.48 (m, 3H), 7.35 (dd, 1H), 6.92 (d, 1H), 3.94 (s, 3H), 3.19 (br s, 4 H), 2.73 (br s, 4H), 2.43 (s, 3H), 2.39 (s, 3H).

10

### Example 2

#### 4-Methoxy-3-(4-methyl-1-piperazinyl)-N-(4-bromophenyl)benzamide

15 4-Bromoaniline (0.260g, 1.51 mmol) was dissolved in toluene (10 ml), and was treated with trimethylaluminium (2.0M in toluene) (2.30 ml, 4.53 mmol) with stirring under argon. After 0.25h, a solution of the product from description 1 (0.400g, 1.51 mmol) in toluene (10 ml) was added. The mixture was then heated to 80°C. After 2h, the reaction mixture was allowed to cool, and was poured into a slurry of silica-gel (~10g) in  
20 dichloromethane (40 ml). The mixture was then stirred carefully until effervescence ceased and filtered. The filter pad was then washed with 20%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  (400ml) and the filtrate was evaporated under reduced pressure to give a brown oil, which was purified by silica-gel chromatography (10%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  as eluant) to give the title compound as a colourless oil (0.475g, 78%), that crystallised on standing.

25

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (s, 1H), 7.60-7.45 (m, 6H), 6.88 (d, 1H), 3.93 (s, 3H), 3.15 (br s, 4H), 2.65 (br s, 4 H), 2.38 (s, 3H)

### Example 3

#### 30 4-Methoxy-3-(4-methyl-1-piperazinyl)-N-[3-methyl-4-(4-pyridyl)phenyl]benzamide

The product from example 1 (0.150g, 0.360mmol), 4-pyridylboronic acid (0.044g, 0.360mmol), and tetrakis(triphenylphosphine)palladium(0) (0.025g) were dissolved in DME (8 ml), and sodium carbonate (0.212g, 2.00mmol) in water (2 ml) was added. The  
35 mixture was then heated to reflux under argon. After 20 h, further amounts of palladium catalyst (0.025g), and 4-pyridylboronic acid (0.030g, 0.244mmol) were added. After reflux was continued for a further 1h, the reaction mixture was allowed to cool, and was

partitioned between dichloromethane and water. The aqueous layer was then extracted with dichloromethane (1X), and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to give a brown oil, which was purified by silica-gel chromatography (10%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  as eluant) to give the title compound as a pale yellow oil (0.116g, 77%), which was crystallised from 60-80 petrol/diethyl ether.

m.pt 110-111°C

$^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ ),  $\delta$  8.62 (dd, 2H), 7.90 (s, 1H), 7.65-7.40 (m, 4H), 7.25 (m, 3H), 6.90 (d, 1H), 3.93 (s, 3H), 3.18 (br s, 4H), 2.65 (br s, 4H), 2.40 (s, 3H), 2.30 (s, 3H).

#### Example 4

4-Methoxy-3-(4-methyl-1-piperazinyl)-N-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl) (1,1'-biphenyl)]benzamide

n-Butyllithium (1.6M in hexanes) (8.36 ml, 0.013 mol) was added dropwise at -90 to -100°C to a stirred solution of the product from Example 1 (0.450g, 1.11 mmol) in dry THF (20 ml) over 20 minutes. The reaction mixture was kept at -90°C for 0.5h, before being allowed to warm to -78°C, and was kept at -78°C for a further 1h, before being allowed to warm to room temperature. The reaction mixture was then stirred at room temperature overnight, before being treated with water (5 ml). After a further 2h stirring at room temperature, the reaction mixture was evaporated under reduced pressure and dried *in vacuo*. The resultant yellow solid was then purified by silica-gel chromatography (10%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) to give the derived phenylboronic acid (0.090g) as an off-white solid.

The phenylboronic acid (0.075g, 0.203mmol) was then dissolved in DME (5 ml) and treated with 3-(4-Bromo-3-methylphenyl)-5-methyl-1,2,4-oxadiazole (0.051g, 0.203mmol) (E.P. 0 533 268 A1). A solution of sodium carbonate (0.065g, 0.609mmol) in water (5 ml) was added. The mixture was then flushed with argon and  $\text{Pd}(\text{PPh}_3)_4$  (10 mg) was added. The mixture was heated to reflux under argon. After 20h, the reaction mixture was allowed to cool, and was partitioned between  $\text{CH}_2\text{Cl}_2$  and water. The aqueous layer was then extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to give a brown oil which was purified by prep. t.l.c. (5-10%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  as eluant) to give the title compound as a pale yellow oil (0.029g), which was converted to its oxalate salt. m.pt 124-125°C (oxalate salt)

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)-free base- δ 7.97 (m, 2H), 7.72 (d, 2H), 7.55 (d, 2H), 7.38 (m, 3H), 7.27 (s, 1H), 6.91 (d, 1H), 3.94 (s, 3H), 3.19 (br s, 4H), 2.73 (br s, 7H), 2.40 (s, 3H), 2.36 (s, 3H).

5 **Example 5**

**4-Methoxy-3-(4-methyl-1-piperazinyl)-N-(4-cyclohexylphenyl)benzamide**

The title compound was prepared from 4-cyclohexylaniline (0.19g, 1.1mmol) and the product from description 1 (0.29g, 1.1mmol) using the method described for example 2.

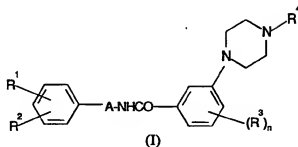
10 Yield 0.13g, 29%.

m.pt 146-148°C

15 <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.71 (s, 1H), 7.59-7.36 (m, 4H), 7.20 (d, 2H), 6.90 (d, 1H), 3.92 (s, 3H), 3.12 (br s, 4H), 2.75-2.41 (m, 5H), 2.35 (s, 3H), 1.98-1.54 (m, 5H), 1.51-1.11 (m, 5H)

## CLAIMS:

1. A compound of formula (I) or a salt thereof:



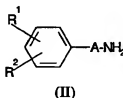
in which

- $R^1$  is optionally substituted phenyl or an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur or  $R^1$  is hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ cycloalkyl,  $C_{1-6}$ alkoxy, hydroxy $C_{1-6}$ alkyl, acyl, nitro, trifluoromethyl, cyano,  $SR^5$ ,  $SOR^5$ ,  $SO_2R^5$ ,  $SO_2NR^5R^6$ ,  $CO_2R^5$ ,  $CONR^5R^6$ ,  $CONR^5(CH_2)_pCO_2R^6$ ,  $NR^5R^6$ ,  $NR^5CO_2R^6$ ,  $CR^5=NOR^6$ , where  $R^5$  and  $R^6$  are independently hydrogen or  $C_{1-6}$ alkyl and p is 1 to 3;
- $R^2$  is hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, hydroxy $C_{1-6}$ alkyl, acyl, nitro, trifluoromethyl, cyano,  $SR^5$ ,  $SOR^5$ ,  $SO_2R^5$ ,  $SO_2NR^5R^6$ ,  $CO_2R^5$ ,  $CONR^5R^6$ ,  $CONR^5(CH_2)_pCO_2R^6$ ,  $NR^5R^6$ ,  $NR^5CO_2R^6$ ,  $CR^5=NOR^6$ , where  $R^5$ ,  $R^6$  and p are as defined for  $R^1$ ;
- $R^3$  is hydrogen, halogen, hydroxy,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy;
- $R^4$  is hydrogen or  $C_{1-6}$ alkyl;
- A is a bond or an acyclic hydrocarbon chain having 1 to 6 carbon atoms; and n is 1 or 2.
2. A compound according to claim 1 in which  $R^1$  is halogen, cyclohexyl, optionally substituted pyridyl or optionally substituted phenyl.
3. A compound according to claim 2 or 3 in which  $R^2$  is hydrogen or  $C_{1-6}$ alkyl.
4. A compound according to any one of claims 1 to 3 in which  $R^3$  is  $C_{1-6}$ alkoxy.
5. A compound according to any one of claims 1 to 4 in which  $R^4$  is  $C_{1-6}$ alkyl.
6. A compound according to any one of claims 1 to 5 in which A is a bond.
7. A compound according to claim 1 which is :
- 4-methoxy-3-(4-methyl-1-piperazinyl)-N-(4-bromo-3-methylphenyl)benzamide,  
 4-methoxy-3-(4-methyl-1-piperazinyl)-N-(4-bromophenyl)benzamide,  
 4-methoxy-3-(4-methyl-1-piperazinyl)-N-[3-methyl-4-(4-pyridyl)phenyl]benzamide,

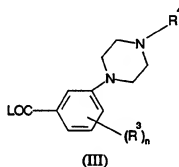


4-methoxy-3-(4-methyl-1-piperazinyl)-N-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)  
(1,1'-biphenyl)]benzamide, or  
4-methoxy-3-(4-methyl-1-piperazinyl)-N-(4-cyclohexylphenyl)benzamide,  
or pharmaceutically acceptable salts thereof.

- 5 8. A process for the preparation of a compound of formula (I) which comprises  
(a) reaction of a compound of formula (II):

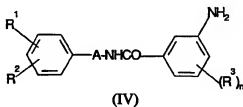


- 10 in which R¹, R² and A are as defined in formula (I), with a compound of formula (III):

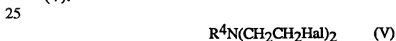


- 15 in which R³, R⁴ and n are as defined in formula (I) and L is a leaving group; or

- (b) reaction of a compound of formula (IV):

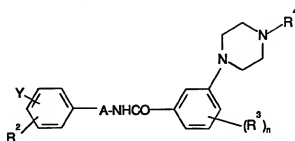


- 20 in which R¹, R², R³, A and n are as defined in formula (I) with a compound of formula  
(V):



in which R⁴ is as defined in formula (I) and Hal is halogen, or

(c) reaction of a compound of formula (VI):



5

(VI)

in which  $R^2$ ,  $R^3$ ,  $R^4$ , A and n are as defined in formula (I) and Y is halogen or a group -  
 $\text{OSO}_2\text{CF}_3$  with a compound of formula (VII):

10

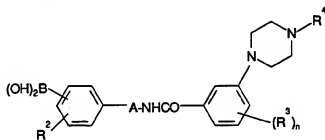


(VII)

in which  $R^1$  is as defined in formula (I), or

15

(d) reaction of a compound of formula (VIII):



20

(VIII)

in which  $R^2$ ,  $R^3$ ,  $R^4$ , A and n are as defined in formula (I) with a compound of formula  
 (IX):

25

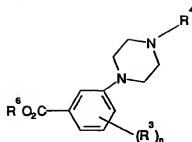


(IX)

in which  $R^1$  is as defined in formula (I) and Y is as defined in formula (VI), or

30

(e) reaction of a compound of formula (II) as defined above with a  
 compound of formula (X):



(X)

5

in which  $R^3$ ,  $R^4$  and  $n$  are as defined in formula (I) and  $R^6$  is  $C_{1-4}$ alkyl in the presence of a trialkylaluminium reagent;

and optionally after any of the above processes:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

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9. A compound according to any one of claims 1 to 7 for use in therapy.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 in association with a pharmaceutically acceptable carrier or excipient.

15

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D295/14 C07D213/40 C07D271/06 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 056 144 (DR. KARL THOMAE GMBH) 21 July 1982 *Page 108-129: claims* ---	1-10
A	EP,A,0 023 569 (DR. KARL THOMAE GMBH) 11 February 1981 *Page 193-225: claims* ---	1-10
A	EP,A,0 533 268 (GLAXO GROUP LIMITED) 24 March 1993 cited in the application *Page 33-39: claims* ---	1-10
A	EP,A,0 533 267 (GLAXO GROUP LIMITED) 24 March 1993 cited in the application *Page 31-35: claims* ---	1-10

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

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Date of the actual completion of the international search

5 January 1995

Date of mailing of the international search report

13. 01. 95

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Authorized officer

Luyten, H

## INTERNATIONAL SEARCH REPORT

Internat. Application No.

PCT/EP 94/02661

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 533 266 (GLAXO GROUP LIMITED) 24 March 1993 cited in the application *Page 24-3-93: claims* ---	1-10
P,X	JOURNAL OF MEDICINAL CHEMISTRY, vol.37, no.15, 22 July 1994 pages 2254 - 2257 JOHN W. CLITHEROW *Page 2255: table 2, compound 11; scheme 3a: step iii* *Page 2256: scheme 4a: step iii* -----	1-10

## INTERNATIONAL SEARCH REPORT

Intern: Application No

PCT/EP 94/02661

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP-A-0056144	21-07-82	DE-A-	3100535	12-08-82
		AU-A-	7929082	22-07-82
		GB-A-	2091729	04-08-82
		JP-A-	57140766	31-08-82
<hr/>				
EP-A-0023569	11-02-81	DE-A-	2928352	15-01-81
		DE-A-	2949259	11-06-81
		DE-A-	3016650	05-11-81
		DE-A-	3016651	05-11-81
		AT-T-	3862	15-07-83
		AU-B-	535924	12-04-84
		AU-A-	6036280	15-01-81
		AT-T-	10632	15-12-84
		EP-A,B	0063826	03-11-82
<hr/>				
EP-A-0533268	24-03-93	AP-A-	303	28-01-94
		AU-A-	2453092	25-03-93
		CA-A-	2078505	19-03-93
		HU-A-	65608	28-07-94
		JP-A-	6116251	26-04-94
		US-A-	5340810	23-08-94
		CN-A-	1076195	15-09-93
<hr/>				
EP-A-0533267	24-03-93	AU-A-	2452892	25-03-93
		AU-A-	2568792	27-04-93
		CA-A-	2078507	19-03-93
		CN-A-	1073430	23-06-93
		WO-A-	9306084	01-04-93
		FI-A-	941261	17-03-94
		JP-A-	6107637	19-04-94
		NO-A-	940974	17-03-94
US-A-	5358948	25-10-94		
<hr/>				
EP-A-0533266	24-03-93	AU-A-	2452992	25-03-93
		CA-A-	2078506	19-03-93
		HU-A-	66319	28-11-94
		JP-A-	6107649	19-04-94
		US-A-	5356893	18-10-94
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